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ORIGINAL REPORT

Targeting ALK With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study

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ABSTRACT

Purpose
Fusions involving the ALK gene are the predominant genetic lesion underlying pediatric anaplastic large cell lymphomas (ALCL) and inflammatory myofibroblastic tumors (IMTs). We assessed the activity of the ALK inhibitor crizotinib in patients who had no known curative treatment options at diagnosis or with relapsed/recurrent disease.

Methods
In this study, 26 patients with relapsed/refractory ALK-positive ALCL and 14 patients with metastatic or inoperable ALK-positive IMT received crizotinib orally twice daily. Study objectives were measurement of efficacy and safety. Correlative studies evaluated the serial detection of *NPM-ALK* fusion transcripts in patients with ALCL.

Results
The overall response rates for patients with ALCL treated at doses of 165 (ALCL165) and 280 (ALCL280) mg/m^2 were 83% and 90%, respectively. The overall response rate for patients with IMT (treated at 100, 165, and 280 mg/m^2/dose) was 86%. A complete response was observed in 83% (five of six) of ALCL165, 80% (16 of 20) of ALCL280, and 36% (five of 14) of patients with IMT. Partial response rates were 0% (none of six), 10% (two of 20), and 50% (seven of 14), respectively. The median duration of therapy was 2.79, 0.4, and 1.63 years, respectively, with 12 patients ceasing protocol therapy to proceed to transplantation. The most common drug-related adverse event was decrease in neutrophil count in 33% and 70% of the ALCL165 and ALCL280 groups, respectively, and in 43% of patients with IMT. Levels of *NPM-ALK* decreased during therapy in most patients with ALCL.

Conclusion
The robust and sustained clinical responses to crizotinib therapy in patients with relapsed ALCL and metastatic or unresectable IMT highlight the importance of the ALK pathway in these diseases.

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INTRODUCTION

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase known to be oncogenically activated either by chromosomal translocations, amplifications, or point mutations within the kinase domain.[1] ALK was first described as part of a genetic rearrangement resulting in an oncoprotein with high *ALK* kinase activity in a subset of anaplastic large cell non-Hodgkin's lymphoma (ALCL), a malignancy that predominantly occurs in children.[2] Subsequently, translocations involving the *ALK* gene were described in nearly half of inflammatory myofibroblastic tumors (IMTs),[3-5] a rare mesenchymal malignancy that also tends to occur primarily in children and adolescents. IMTs frequently arise in the lung or abdominal cavity and are resistant to conventional chemotherapy and radiation approaches. Complete surgical resection is the only known curative treatment. Although previous data showed that approximately 50% of these tumors harbor a translocation involving the *ALK* gene, more recent data identified *ALK* fusions with noncanonical breakpoints in additional subsets of IMTs, suggesting a dependence on *ALK* signaling in

ASSOCIATED CONTENT

Appendix
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most of these rare tumors.[6] The paramount discovery of *ALK* fusions in a subset of patients with non–small cell lung cancer drove early-phase clinical studies of crizotinib,[7] an ALK-ROS1-MET small molecule inhibitor, and robust objective responses led to expedited US Food and Drug Administration approval of this first-in-class ALK inhibitor.[8] Since then, several ALK inhibitors have been in clinical development to overcome the inevitable challenges of acquired drug resistance.[9-12]

We previously reported the results of a phase I dose-escalation trial of crizotinib in children with relapsed/refractory cancer, demonstrating that this agent was well tolerated up to a recommended phase II dose (RP2D) of 280 mg/m^2, nearly twice that of the adult standard dose.[13] Additionally, at the completion of the dose escalation/finding phase, there were phase II expansion cohorts for the ALK-driven childhood malignancies ALCL and neuroblastoma and a separate cohort for other ALK-driven malignancies, including IMT. This report describes the outcome for the ALCL cohort and for patients with IMT who were enrolled through the course of the trial.

METHODS

Study Design

A Simon two-stage design was used to evaluate the activity of crizotinib monotherapy in patients with recurrent ALCL. In the absence of available enrollment openings in the phase I, trial, patients with recurrent ALCL or unresectable IMT could enroll at one dose level below that actively accruing to the phase I trial or at the starting dose level if dose escalation had not yet occurred. Enrollment of patients with IMT could continue during the phase II for patients with ALCL. Patients with ALCL who were enrolled in the phase I trial and treated at doses equivalent to the maximum tolerated dose or RP2D were included in the phase II analyses. Secondary objectives included exploration of the relationship between minimal residual disease using reverse transcriptase polymerase chain reaction (RT-PCR) and clinical response to crizotinib in patients with ALCL. The trial was approved by institutional review boards and all patients or their parent/legal guardian signed informed consent; assent was obtained per institutional guidelines.

Patients

Patients with recurrent ALCL or unresectable IMT for > 12 months and younger than 22 years were eligible; patients with IMT were eligible without prior exposure to therapeutic agents. Confirmation of diagnosis was based on the pathology report. All patients had to harbor an underlying ALK fusion, detected either by immunohistochemistry or by fluorescence in situ hybridization assays that were Clinical Laboratory Improvement Amendments certified. Standard Children's Oncology Group (COG) criteria for performance status, as well as bone marrow (BM), and renal and liver function were used.[13]

Toxicity Evaluation

Adverse event (AE) attribution was graded according to the Common Terminology Criteria for Adverse Events version 4.0. The relative frequency of each AE considered possibly, probably or likely related to crizotinib was estimated as the proportion of all toxicity-evaluable cycles in which such toxicity was observed.

Response Assessment

Objective responses had to be sustained for a minimum of two consecutive imaging evaluations at least 4 weeks apart. Imaging studies for patients with a reported objective response or for those with prolonged stable disease (at least six cycles) underwent central radiographic review.

This protocol was developed using the International Working Group response criteria for malignant lymphoma[14] and the revised Cheson criteria[15] for response assessment; patients with ALCL also had their disease evaluated using the Lugano Classification applied during central review as a retrospective scoring of response.[16] In contrast to the earlier Cheson criteria, which relied primarily on ^{18}F-labeled fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) to assess treatment response, the Lugano Classification also incorporates computed tomography (CT) and/or magnetic resonance imaging-based decreases in tumor size into response criteria. The recently proposed international pediatric non-Hodgkin lymphoma response criteria[17] are similar to the Lugano criteria and also apply additional subclassifications, including complete response (CR) unconfirmed, for cases that would otherwise meet CR criteria, except for a residual mass that is FDG negative. We have presented our findings using the Lugano classification. In only two of 26 ALCL cases were differences in response classification noted, both of which were partial responses (PRs), on the basis of the Lugano classification and CR unconfirmed on the basis of the international pediatric non-Hodgkin lymphoma response criteria.

Patients with IMTs had their disease evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. ^{18}F-FDG PET/CT imaging was performed at the treating institutions' discretion.

Correlative Biology Studies

In patients with ALCL, serial assessments of the *NPM-ALK* fusion transcript were evaluated in one laboratory by quantitative RT-PCR. Baseline BM and peripheral blood (PB) samples were obtained, as were blood samples on day 15 of cycle 1, day 1 of cycle 2, and then once during each subsequent cycle. Quantitative RT-PCR (qRT-PCR) was performed and the normalized copy numbers were expressed as copy numbers of *NPM-ALK* per 10^4 copies of *ABL*, as previously published.[18]

RESULTS

Patients

Twenty-six patients with ALCL and 14 patients with IMT enrolled in the study between September 2009 and October 2015; all were eligible and evaluable for response. Of the 26 patients with ALCL, 16 (62%) were enrolled in the phase I study. Six of these patients were treated at a dose of 165 mg/m^2 and 10 were treated at the RP2D of 280 mg/m^2. All 10 patients treated at the RP2D in phase I of the study were included in the phase II study. The remaining 10 patients with ALCL were specifically enrolled in the phase II expansion cohort and treated at the RP2D.

Eight (57%) of the 14 patients with IMT were enrolled in the dose-escalation portion of this study. One was treated with 100 mg/m^2/dose, one with 165 mg/m^2/dose, and six were treated at the RP2D. The remaining six patients were enrolled in the phase II study and treated at the RP2D. Results for patients with IMT are presented as a pooled cohort because the patients treated at the 100 and 165 mg/m^2 doses had similar toxicity and responses as those treated at the RP2D.

Patients with ALCL are presented in two groups (Table 1): those treated at the 165 mg/m^2 dose (ALCL165) and those treated at the 280 mg/m^2 dose (ALCL280). Patients enrolled in ALCL280 tended to be older (median age, 12.2 years) compared with patients in the ALCL165 group (median age, 5.9 years) and patients with IMT (median age, 7.0 years). All patients with ALCL had received

Table 1. Characteristics of the Patients at Baseline

Characteristic	ALCL165 (n = 6)	ALCL280 (n = 20)	IMT (n = 14)*
	Cohort		
Age at enrollment, years, median (min, max)	5.9 (3.7,13.4)	12.2 (6.1,20.8)	7.0 (2.0,13.5)
Sex			
Female	1 (17)	7 (35)	9 (64)
Male	5 (83)	13 (65)	5 (36)
Race			
White	4 (67)	10 (50)	10 (71)
Black	0 (0)	5 (25)	1 (7)
Asian	1 (17)	1 (5)	0 (0)
Unknown	1 (17)	4 (20)	3 (21)
No. of prior therapies			
0	0 (0)	0 (0)	2 (14)
1-2	5 (83)	16 (80)	9 (64)
3-4	0 (0)	2 (10)	3 (21)
5-6	1 (17)	2 (10)	0 (0)
No. of patients with at least one prior therapy			
Chemotherapy	6 (100)	20 (100)	4 (29)
Radiotherapy	0 (0)	1 (5)	0 (0)
Stem-cell transplant	1 (17)	1 (5)	0 (0)
Surgery	1 (17)	1 (5)	8 (57)
Anti-inflammatory	0 (0)	0 (0)	4 (29)
Brentuximab	0 (0)	1 (5)	0 (0)
MoAb NOS	1 (17)	2 (10)	0 (0)
Disease status			
Evaluable	0 (0)	4 (20)	2 (14)
Measurable	6 (100)	16 (80)	12 (86)

NOTE. Data given as No. (%) unless otherwise indicated.
Abbreviations: ALCL, anaplastic large cell lymphoma; IMT, inflammatory myofibroblastic tumor; MoAb, monoclonal antibody; NOS, not otherwise specified.
*Patients with IMT were treated at dose levels of 100 (n = 1), 165 (= 1), and 280 (n = 12) mg/m^2 per dose.

at least one prior therapy, as had most (86%) of the patients with IMT. All patients with ALCL received at least one course of chemotherapy, but only four (29%) of the patients with IMT had done so. The most common prior therapy for patients with IMT was surgery, which occurred in eight of the 14 patients (57%). There was one patient in ALCL280 who previously received therapy with brentuximab.

Safety

At least one grade 3 or 4 AE occurred in 83% of patients in ALCL165, 100% of patients in ALCL280, and 71% of patients with IMT. Grade 3 or 4 AEs that were possibly, probably, or definitely related to the study drug occurred in 33%, 85%, and 57% of the study cohorts, respectively (Appendix Table A1, online only). The most common grade 3 or 4 drug-related AE was a decrease in neutrophil count. At least one neutrophil count decrease was observed in 33% of patients in ALCL165, 70% of patients in ALCL280, and 43% of patients with IMT.

Clinical Activity

The objective response rate for patients with ALCL included in the Simon's two-stage design at the RP2D was 90% (95% CI, 68 to 99). The objective response rate (Table 2) for patients with ALCL treated at 165 mg/m^2/dose was 83% (95% CI, 36 to 99.6) and for patients with IMT was 86% (95% CI, 57 to 98). The median duration of therapy was 2.8, 0.4, and 1.6 years for ALCL165, ALCL280, and patients with IMT, respectively. For the 26 patients with ALCL, there was complete concordance between central review and site evaluation of response for 20 patients; three patients with a site determination of PR were determined to be CRs by central review, two patients with CR by site determination had a PR by central review, and a one patient with a site-determined PR was determined to have stable disease on central review.

The six patients with ALCL treated at the 165 mg/m^2 dose all had measurable disease; five had evidence of initial response by 4 weeks after initiating treatment, with two CRs and three PRs (Fig 1). The sixth patient had stable disease for > 30 cycles. Eighteen of 20 patients with ALCL treated at the RP2D had a CR or PR, and 13 of these patients had the first response within 4 weeks of initiating treatment (Fig 1). The remainder had initial responses within 5 weeks (n = 4) and 8 weeks (n = 1) of initiating treatment. Figure 2A shows the ^{18}F-FDG PET-avid disease at time of enrollment and the brisk resolution of abnormal metabolic activity after one cycle of therapy. At the time of this report, two patients with ALCL remain on protocol therapy. Patients with ALCL came off therapy after experiencing AEs (n = 2), site determination of progressive disease (n = 3), at physician or parent discretion (n = 16), failure to meet protocol criteria to continue (n = 1), noncompliance (n = 1), and being lost to follow-up (n = 1). Among the 16 patients

Table 2. Clinical Activity in Patients Treated With Crizotinib

Outcome	ALCL165 (n = 6)	ALCL280 (n = 20)	IMT (n = 14)
Best overall response			
Complete response	5 (83)	16 (80)	5 (36)
Partial response	0	2 (10)	7 (50)
Stable disease	1 (17)	2 (10)	2 (14)
Progressive disease	0	0	0
Therapy duration, years, median (95% CI)	2.79 (0.31 to n/a)	0.4 (0.18 to 1.0)	1.63 (0.55 to 2.30)
Time to first PR/CR, days, median (95% CI)	26.5 (24 to n/a)	27 (25 to 29)	28.5 (27 to 134)

NOTE. Data given as No. (%) unless otherwise indicated.
Abbreviations: ALCL, anaplastic large cell lymphoma; CR, complete response; IMT, inflammatory myofibroblastic tumor; n/a, not applicable; PR, partial response.

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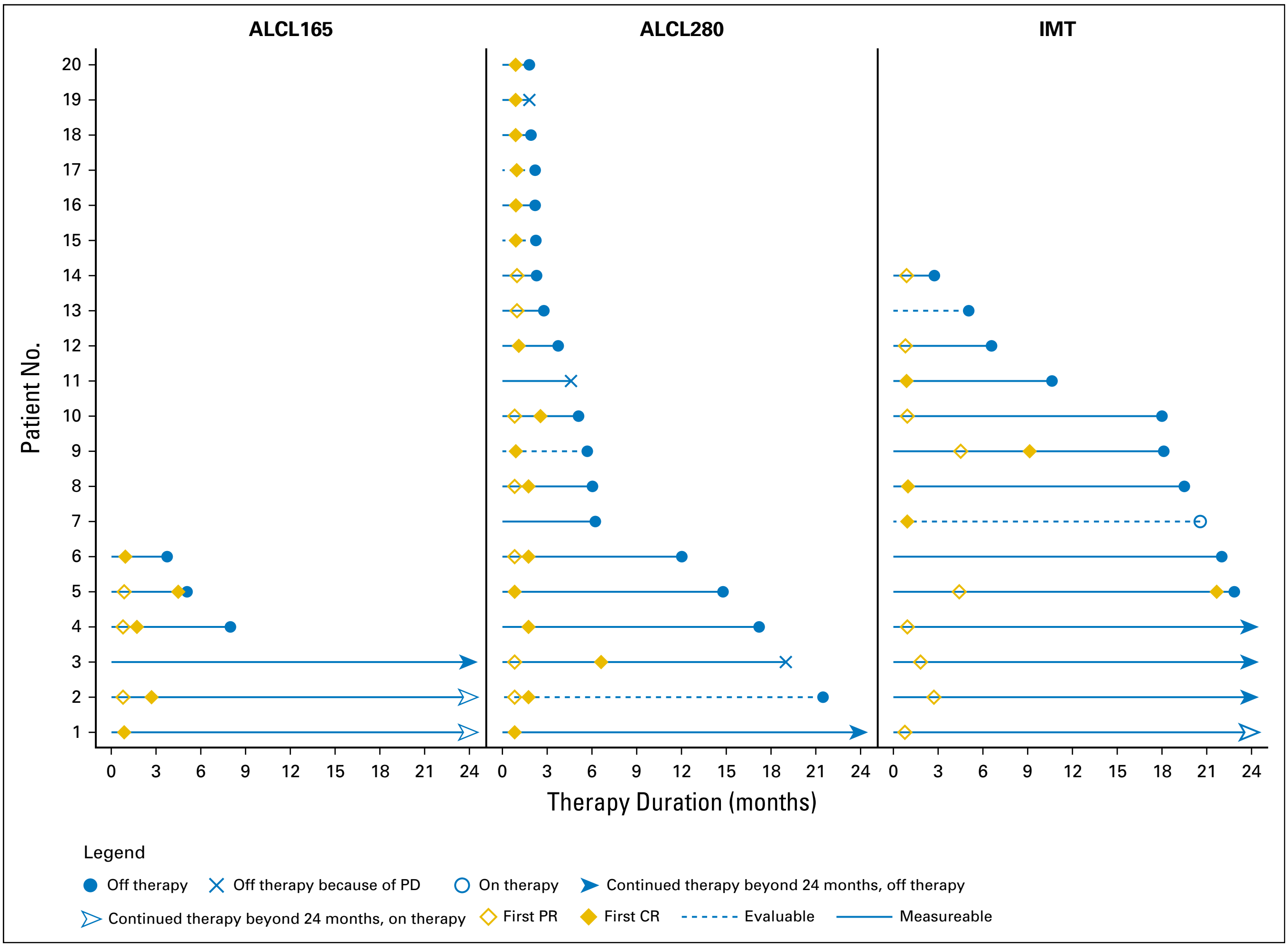

Fig 1. Response characteristics in patients with ALK-translocated ALCL and IMT who are receiving crizotinib. The three panels show response onset and duration for patients in the ALCL165, ALCL280, and IMT groups treated with crizotinib. The length of the bar shows the time until the patient had a CR or PR, along with the duration of response up to 24 months. Therapy duration exceeded 24 months for three patients at the ALCL165 dose (71.24, 65.75, and 58.88 months, respectively), one patient at the ALCL280 dose (39.88 months), and four patients with IMTs (63.45, 41.59, 27.58, and 25.08 months, respectively). ALCL, anaplastic large cell lymphoma; ALCL165, patients with anaplastic large cell lymphoma receiving a 165 mg/m^2 dose of crizotinib; ALCL280, patients with anaplastic large cell lymphoma receiving a 280 mg/m^2 dose of crizotinib; CR, complete response; IMT, inflammatory myofibroblastic tumor; PD, progressive disease; PR, partial response.

who were removed from protocol therapy, 12 did so to proceed to stem-cell transplantation, two patients refused further treatment, and two patients refused continued treatment while in the study but continued on commercial crizotinib. One of the patients removed from protocol therapy because of AE (neutropenia) also proceeded to stem-cell transplantation after the first cycle of crizotinib.

Among 12 patients with IMT who had a CR or PR, seven had the first response within 4 weeks, two within 8 weeks, and three within 20 weeks of initiating treatment (Fig 1). Of the 14 patients with IMT, three had concurrent PET imaging: two patients had a PR by RECIST criteria at 4 weeks, a CR by functional metabolic imaging at the same time point, but never achieved an anatomic CR; one patient had a PR at 12 weeks and CR at 40 weeks by RECIST criteria, but a CR by ^{18}F-FDG PET imaging at 12 weeks. One patient had only ^{18}F-FDG PET/CT imaging and response assessment was based on PET. At the time of this report, two patients remain on protocol therapy. Patients with IMT came off therapy because of AEs including repeated grade 4 absolute neutrophil count and lower extremity edema (n = 4), or because of physician or parent discretion (n = 5), completion of 24 cycles of therapy (n = 1), and noncompliance (n = 2). Figure 2B shows a representative patient with multiple measurable, FDG-avid pulmonary nodules who had a PR by RECIST (residual measurable pulmonary nodules) but a CR by ^{18}F-FDG PET after cycle 1 of therapy, emphasizing the potential importance of functional imaging in assessing response to molecularly targeted agents.

ALK-Fusion Burden in Patients With ALCL

At the time of this report, qRT-PCR data were obtained from 24 patients with a total of 282 samples (21 pretherapy BM aspirates, 25 pretherapy PB samples, two post-therapy BM samples, and 234 post-therapy PB samples collected monthly). Of the 24 patients, paired samples from pre-enrollment BM and PB samples were available for 18 patients (Fig 3A). Of the 18 paired

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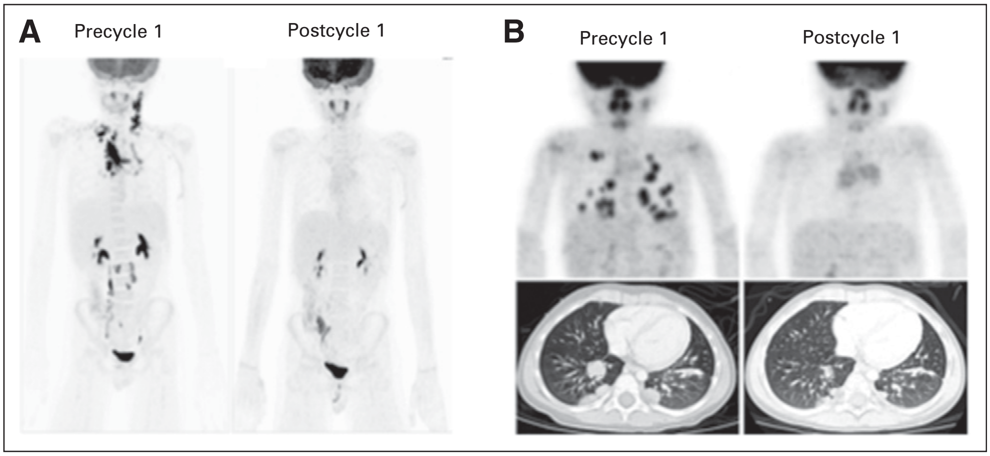

Fig 2. Images of representative patient. (A) Coronal maximum projection intensity positron emission tomography (PET) images taken after administration of ^{18}F-labeled fluorodeoxyglucose (^{18}F-FDG) show multiple sites of FDG-avid metabolically active anaplastic large cell lymphoma tumor at baseline, including left cervical chain, mediastinal, retroperitoneal, and iliac chain lymph nodes. After one cycle of therapy, pathologic FDG uptake resolved completely (uptake in the right lower quadrant reflects physiologic FDG accumulation in distal small bowel, confirmed on coregistered and fused PET/computed tomography (CT) images (not shown). (B) Baseline whole-body ^{18}F-FDG-PET and chest CT images show multiple FDG-avid pulmonary nodules, confirmed by biopsy specimen to be IMT. After one cycle of therapy, no residual abnormal FDG accumulation is seen (metabolic complete response [CR]). The lesions also decreased significantly in size, on CT image, meeting criteria for partial response, but not CR.

samples, five patients had no quantifiable levels of *NPM-ALK* in either the BM or PB. In 13 of the 18 paired samples, quantifiable *NPM-ALK* was observed in both the BM and PB. Notably, the levels of *NPM-ALK* in BM were lower than that observed in PB in 10 of 13 paired samples. qRT-PCR levels of *NPM-ALK* were available for 24 patients at day 15 of cycle 1 and either day 1 of cycle 2 or once during each subsequent cycle. Except for one patient, all remaining patients (n = 23) showed a decrease in the first month, which continued over the subsequent cycles (Fig 3B).

DISCUSSION

Current clinical trial approaches in rare diseases are challenging. Increased attention is being placed on the development of targeted agents for patients with cancers that share a molecular etiology to expedite clinical testing of potentially active drugs for rare indications. In this trial, pediatric patients with solid and lymphoid cancers were grouped based on activating lesions in the *ALK* oncogene.

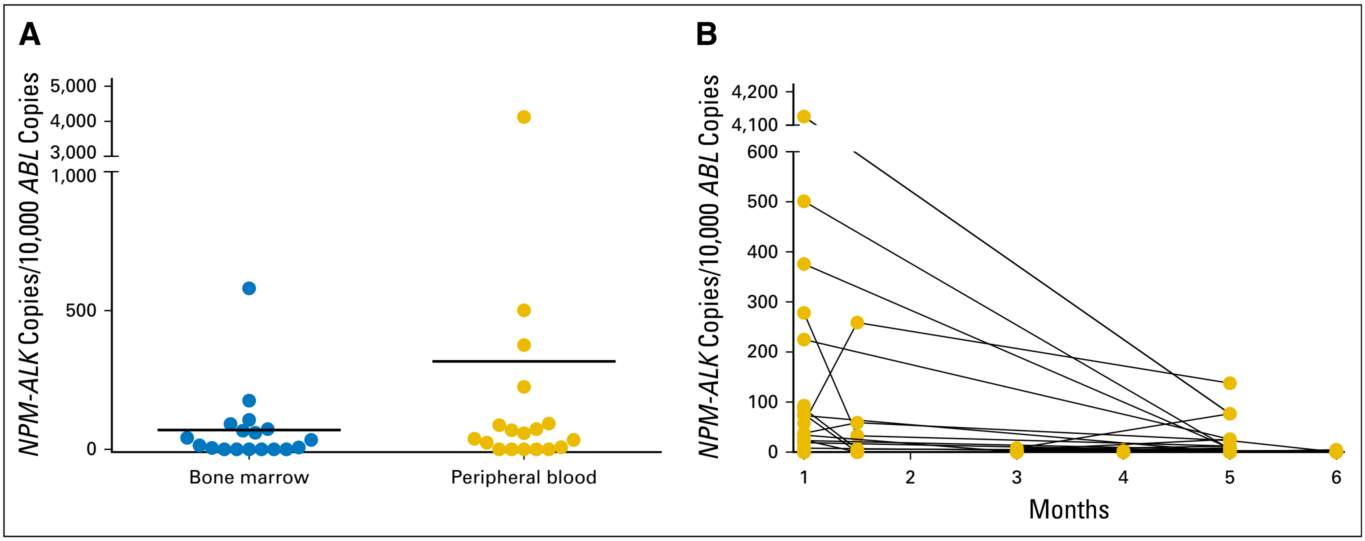

Fig 3. Detection and quantification of *NPM-ALK* in bone marrow (BM) and peripheral blood (PB). (A) *NPM-ALK* fusion transcript was quantified in 18 paired pre-enrollment BM and PB samples using quantitative reverse transcriptase polymerase chain reaction. The blue circles represent the *NPM-ALK* levels in BM, and the gold circles represent the *NPM-ALK* levels in PB. Of the 18 paired samples, five patients had no quantifiable levels of *NPM-ALK* in BM, and PB. Only one patient had quantifiable *NPM-ALK* level in PB but not in BM. The levels of *NPM-ALK* in BM are lower than in PB in most of the paired samples (10 of 13). (B) The change of *NPM-ALK* transcript levels in the PB over 6 months of treatment is represented for 23 patients for whom *NPM-ALK* was detected and quantified at the time of enrollment. Except for one patient, *NPM-ALK* transcript levels decreased as early as 1 month of treatment. Thirteen patients had a reduction > 75% of *NPM-ALK* levels in PB within the first month. BM, bone marrow; PB, peripheral blood.

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Notable objective and sustained responses were observed in patients with *ALK* fusion-positive ALCL and IMT, establishing a precedent in pediatric oncology for studying the early-phase activity of a targeted agent in a biomarker-selected and histology-independent cohort of patients.

The *ALK* oncogene has proven to be of importance across histologically diverse tumors, and is a bona fide mediator of oncogenesis across several pediatric malignancies.[1] ALCLs represent a subset of peripheral T-cell lymphomas and account for up to 15% of all childhood lymphomas. The vast majority of pediatric cases harbor the characteristic *ALK* gene fusion,[19] and it is reasoned that ALK-negative ALCLs are a nonoverlapping entity.[20] Optimal therapy for children and adolescents with advanced stage ALCL remains unknown, and progression while receiving chemotherapy is associated with a poor prognosis despite aggressive salvage regimens, including allogeneic transplantation.[21,22] Recent efforts to improve treatment strategies by replacing vincristine with weekly vinblastine in maintenance had no impact on survival.[23] There is no standard of care at time of relapse, and although vinblastine monotherapy is an active agent,[24] it is an empirical cytotoxic therapy administered intravenously. Developing more rational targeted therapies to improve the outcome for children with ALCL is essential.

In this trial, where crizotinib was administered orally twice daily in 28-day cycles as a single agent for an indefinite duration, patients with relapsed ALCL achieved an objective response rate of 90%. The rate, type, and duration of response vastly exceeded those typically observed in any early-phase clinical trial for children with relapsed/refractory cancer, possibly owing to the less complex genomic landscape of ALCL and the addiction to a single driver oncogene. Correlation between response and histologic subtype could not be made, although the significance of morphologic variant and outcome is not known at time of relapse. A robust prognostic indicator at time of diagnosis for children with ALCL is the level of NPM-ALK transcript in the BM, as well as antibody titers to ALK in the plasma.[18,25] We obtained qRT-PCR data on pre- and post-therapy BM and PB samples at numerous time points in most patients and, in available paired samples, showed that detection of circulating tumor-derived NPM-ALK transcript decreased with disease response.

Although aberrant ALK activation is an oncogenic driver in cancers as disparate as lymphomas and non–small cell lung cancer, durability of response differs vastly and is tissue-context dependent. Early relapse after discontinuation of therapy has been reported in one adult and one pediatric patient with ALCL,[26] and although this was not directly assessed within the context of this study because we do not have follow-up data for patients who have discontinued ALK inhibitor therapy, with the exception of those who pursued stem-cell transplantation, this should be investigated prospectively. Notably, the onset and durability of responses do not seem to be dose dependent, with objective and sustained responses seen at the lower (165 mg/m^2) and higher (280 mg/m^2) dosing of crizotinib in ALCL. The robust and sustained activity observed in this trial has provided the rationale for the currently accruing COG pilot phase II study (NCT01979536) combining crizotinib at 165 mg/m^2 with conventional chemotherapy in newly diagnosed patients with ALCL.

In the cohort of patients with ALK-positive unresectable IMTs, ALK inhibition was a highly effective therapy and supports consideration of frontline therapy with crizotinib, a strategy that could be also be relevant to adults with this rare disease.[27] Numerous ALK fusion partners have been identified that may influence both histologic features and response to targeted therapy. Interestingly, these tumors do not respond uniformly to crizotinib and may benefit from the higher dosing, though most patients on this trial had at least a PR by 4 weeks; it is noteworthy that the three patients who also had imaging with FDG-PET demonstrated a complete metabolic response early on in therapy, and either never achieved a complete anatomic response or did so much later in the course of treatment. This discordance suggests there may be underlying biologic factors influencing the differential sensitivity to ALK-targeted therapy, and highlights the role of functional imaging in assessing response to targeted therapy and considerations for integrating classic RECIST and metabolic criteria into trials evaluating these agents.

A similar discordance between PET and anatomic response was also observed in the ALCL cohort, where 11 of 26 patients initially had complete metabolic responses despite only meeting criteria for stable disease or PR on the basis of anatomic response. Nine of the 11 patients eventually achieved both metabolic and anatomic CR; the two patients who remained in PR were FDG(−) but still had measurable disease by CT. In the context of an oncogene addiction such as NPM-ALK, molecularly targeted agents may impart significant effects on cellular metabolism while not immediately resulting in tumor shrinkage.[28] Estimating the metabolic activity of tumor, together with conventional anatomic measures of response, will likely result in a more precise assessment of response to *ALK* kinase inhibition, as has been shown for therapeutic responses to EGFR kinase inhibitors in patients with EGFR-mutant non–small cell lung cancer.[29]

The robust and sustained clinical responses to crizotinib in patients with relapsed or refractory ALK-driven ALCL and IMT highlight the importance of this oncogene and the sensitivity to ALK inhibition in these diseases.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Frequencies of Grade 3 or 4 Adverse Events Possibly, Probably, or Definitely Related to Study Drug

	ALCL165		ALCL280		IMT		Total	
Adverse Event	No. of Patients	No. of Events	No. of Patients	No. of Events	No. of Patients	No. of Events	No. of Patients	No. of Events
Alanine aminotransferase increased	0	0	1	1	0	0	1	1
Anemia	0	0	1	1	0	0	1	1
Diarrhea	0	0	1	1	1	1	2	2
Edema limbs	0	0	0	0	1	1	1	1
Febrile neutropenia	0	0	1	1	0	0	1	1
Infective myositis	0	0	1	1	0	0	1	1
Lymphocyte count decreased	0	0	1	1	0	0	1	1
Neutrophil count decreased	2	5	14	33	6	28	22	66
Platelet count decreased	0	0	1	1	.	.	1	1
Sinus bradycardia	0	0	0	0	1	1	1	1
Skin and subcutaneous tissue disorder	0	0	1	1	0	0	1	1
Skin infection	0	0	1	1	0	0	1	1
Vomiting	0	0	1	1	0	0	1	1
WBC count decreased	0	0	3	4	0	0	3	4
Total	2	5	27	47	9	31	38	83

Abbreviations: ALCL, anaplastic large cell lymphoma; IMT, inflammatory myofibroblastic tumor.

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